Purple discoloration (~ 1X1 cm) was noted around the injection site was noted in one dog from the mixed micelles group 1 day after the injection. No other venous irritation was observed over a 7 day period.

TESTING FOR VENOUS IRRITATION IN RABBITS (REF IIIQ1) NOTE: THIS WAS PART OF THE SAME STUDY IN DOGS ABOVE

12 NZW rabbits were randomly assigned to 2 test groups (3/sex/group).
Group I: single injection of 1.0 ml [redacted] 15-1788/014 dissolved in mixed micelles in the marginal vein of one ear. Each animal served as own control; 1 ml of physiological saline was injected to the contralateral ear vein.
Group II: 1 ml of mixed micelles alone. Again, this group served as its own control.

The infusion rate was ~ 3.1 ml/min. Ears were examined and graded for irritation 1-3, 6-10 and 13-14 days after treatment.

RESULTS

The magnitude of irritation was similar between saline-treated ears and the micelle treated ears. The sponsor concluded that the two test articles did not cause significant irritation to rabbit ear veins.

CONCLUSIONS

The sponsor concludes that the ratio of drug component and mixed micelles may result in toxic findings. In the case of undegraded mixed micelles, the toxicity is attributed to the glycocholic acid component. The formation of lysolecithin after partial degradation of the mixed micelles is responsible for the exacerbated toxicity of partially degraded mixed micelles.

COMMENT: The sponsor has mentioned several times that the ratio of glycocholic: lecithin ratio may vary depending upon the particular agent being solubilized in the mixed micelles. Thus, it is not clear if the ratio tested is actually the same as that used in the Cernevit. The monograph is geared to test the general toxicity of the mixed micelle preparation. In a series of tests using Cernivit in rats, rabbits and dogs, results seem to support the safety as described in the various tests with mixed micellar preparations.

SAFETY PHARMACOLOGY

EFFECT OF [redacted] 1701465 ON FREE BEHAVIOR IN DOGS (REF. III F1)

Study performed by [redacted] Dated April 6, 1984. No GLP or QA statement was provided. [redacted] report number: B-101'438

10 female beagle dogs (2/group) were dosed volumes of 0.1, 0.3 and 1 ml/kg fresh ([redacted]17 7465/001) and heat-decomposed [redacted]-17 7465/002) mixed micelles IV at a rate of 5 ml/min in the saphenous vein. The drug-free interval between each infusion was 4 weeks. Dogs were observed continuously over "extended time periods" and changes in free behavior were noted.

There were no findings in gross spontaneous behavioral alterations at the volumes infused. One dog exhibited hypersalivation during the infusion of 1 ml/kg of fresh mixed micelles; no autonomic symptoms were observed.

SUPPRESSION OF TONIC CONVULSIONS ELICITED BY MICE BY PENTYLENETETRAZOL OR MAXIMAL ELECTROSCHOCK: COMPARATIVE EFFECTS OF [redacted]17-7465/001, [redacted] 17-7465/002 AND PROPYLENE GLYCOL

Study performed by [redacted] Dated March 28, 1984. No GLP or QA statement was provided. [redacted] report number: B-101'402

IV treatment of female mice with 0.1, 0.3, 1.0 and 3.0 ml/kg of [redacted] 17-465/000, [redacted] 17-7465/002 and propylene glycol did not protect from tonic convulsions produced by electroshock (50Hz 10 mA for 0.2 sec) or pentylenetetrazol (120 mg/kg IP). Neither chemically nor electrically-induced convulsions in mice were modified by IV pretreatment in the dose range tested with either fresh or decomposed mixed micelles.

EFFECTS ON CARDIOVASCULAR SYSTEM

EFFECT OF FRESH AND ARTIFICIALLY AGED MIXED MICELLES ON SYSTOLIC BLOOD PRESSURE, HEART RATE AND GROSS SPONTANEOUS BEHAVIOR OF CONSCIOUS NORMOTENSIVE DOGS (REF III F3)

Study performed by [redacted] Dated June 28, 1984. No GLP or QA statement was provided. [redacted] report number: B-101'466

8 Female mongrel dogs were evaluated in groups of 4 each. IV doses of 0.01, 0.03, 0.1 and 0.3 ml/kg of both fresh and partially degraded mixed micelles ([redacted] 17-7465/001 and /002). There was a very weak and inconsistent reduction in BP following injection. The peak effect was 8 mmHg occurring 60 minutes after administration of 0.3 ml/kg dose. The HR increased immediately after each administration (peak effect being 18 beats/min) after the highest dose tested. This persisted for 5-10 min.

In the partially aged mixed micelles, no changes in systolic blood pressure, heart rate or gross spontaneous behavior were observed.

PARTIAL HEMODYNAMIC EVALUATION OF [redacted] 17-7465 IN ANESTHETIZED, OPEN-CHEST CATS (REF IIIF4)

Study performed by [redacted] Dated June 25, 1984. No GLP or QA statement was provided. [redacted] report number: B-101'506.

Cats of either sex were anesthetized with pentobarbitone sodium (80 mg/kg IP) and artificially ventilated. Body temperature and blood gases were maintained constant. Both fresh and artificially–aged mixed micelles were tested with propylene glycol for comparison. Drug was administered by rapid bolus injection (1 ml/sec) of doses up to 1 ml/kg. 1 ml/kg was also slowly

injected over a 3 minute period and over a period of 6 h. Infusion rate was doubled every hour from 0.3 ml/kg/h to 2.4 ml/kg/h resulting in a total volume of 4.5 ml/kg infused within 4 h.

Results:
MAP and TPR were reduced dose dependently by the fresh mixed micelles. This was a transient effect exceeding a 1 minute duration only at the highest dose level (5 min). No effects were noted in HR or cardiac output. There was a slight non-statistically significant decrease in myocardial contractile force. Slow injections produced similar findings.

For artificially aged mixed micelles, there were dose-dependent decreased in MAP and TPR which were more marked than with the fresh compound, lasting 8 minutes with the highest dose. There was no change in HR or cardiac output. Myocardial contractile force decreased moderately with the highest dose only. Sponsor estimates that the partially degraded product was approximately 10 times as potent as the fresh preparation.

Propylene glycol had a depressant effect. It decreased MAP, TPR, MCF and HR. Duration of action was less than 5 min at doses less than 0.3 ml/kg, but exceeded 10 minutes following administration of 1 ml/kg. Cardiac output was increased.

Effects appeared to be similar whether infusion was slow or rapid.

CARDIOVASCULAR EFFECTS OF MIXED MICELLES SOLUBILIZER [redacted] 17-7465 IN THREE DIFFERENT ANIMAL SPECIES (REF IIIF4)

Study performed by [redacted] Dated July 5, 1984. No GLP or QA statement was provided. [redacted] report number: B-101'513

CARDIOVASCULAR EFFECTS OF MIXED MICELLES ([redacted] 17-7465/001) IN CHLORALOSE-URETHANE ANESTHETIZED CATS (REF II F5)

Cats of either sex were anesthetized with chloralose-urethane (40:700 mg/kg IP) and artificially ventilated. Body temperature was maintained. This study was proposed to demonstrate whether the fresh mixed micelles used in the experiment precipitate an anaphylactic reaction. 0.66 ml/kg of [redacted] 17-7465/001 was administered IV before and after injection of the H1 receptor blocking agent mepyramine (1 mg/kg IV) and the H2 receptor blocker cimetidine (10 mg/kg IV). To exclude a cholinergic effect [redacted] 17-7465/001 was administered before and after the blocking of the muscarinic receptors by 0.3 mg/kg atropine IV.

Results: [redacted] 17-7465/001 decreased MAP by 55% for approximately 20-30 min and increased HR by 7% for the same period. The effects were slightly inhibited by atropine pretreatment indicating that approximately 15% of the effect may be due to stimulation of muscarinic receptors. Blocking H1 and H2 receptors did not modify the hypotensive effect. Thus, an anaphylactic reaction triggered by [redacted] 17-7465/001 was deemed unlikely. Note: the hypotensive effect in anesthetized cats was not observed in conscious SHR rats and in normotensive rabbits.